04.11.2004

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

GB0412497

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 08 AUG 2004

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

04.11.2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
M
- 5 NOV 2003
LONDON

The Patent Office

1/77

06NOV03 E849776-6 D00245
P01/7700 0.00-0325830.8

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

- 5 NOV 2003

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1.	Your reference	4-33443P1	
2.	Patent application number *(The Patent Office will fill in this part)*	0325830.8	
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND SWITZERLAND 07125487005	
4.	Title of invention	Organic Compounds	
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	Craig Mc Lean Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB 07181522002 ✓	
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)* / Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes	

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	35
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	✓
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig Mc Lean 5th November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew 01403 323069

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

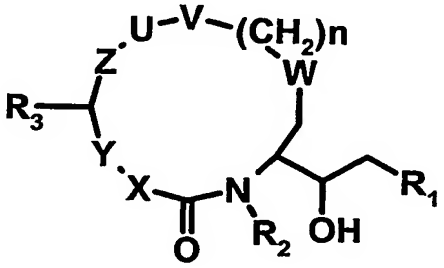
d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

Organic Compounds

The present invention relates to novel macrocyclic compounds, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides compounds of formula I



wherein

R_1 is $CH(R_e)CONR_aR_b$ or $(CH_2)_kNR_cR_d$, wherein

k is 0, 1 or 2,

R_a and R_b, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl,

R_c and R_d, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, chroman-4-yl, 1,2,3,4-tetrahydro-quinolin-4-yl, 1,2,3,4-tetrahydro-naphthalen-1-yl, thiochroman-4-yl, 1,1-dioxo-1lambda*6*-thiochroman-4-yl, isochroman-4-yl, 1,2,3,4-tetrahydro-isoquinolin-4-yl, isothiochroman-4-yl, 2,2-dioxo-2lambda*6*-isothiochroman-4-yl, 2,2-dioxo-1,2,3,4-tetrahydro-2lambda*6*-benzo[c][1,2]thiazin-4-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-benzo[e][1,2]thiazin-4-yl, 2,2-dioxo-3,4-dihydro-2H-2lambda*6*-benzo[e][1,2]oxathiin-4-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-benzo[e][1,2]thiazin-4-yl, 2,3,4,5-tetrahydro-benzo[b]oxepin-5-ylamine or 1,3,4,5-tetrahydro-benzo[c]oxepin-5-ylamine, or

R_a, and R_b, or R_c and R_d, together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidino, morpholino or piperazinyl group, and

R_e is optionally substituted (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl,

R_2 is hydrogen or (C_{1-4})alkyl,

R_3 is hydrogen or an optionally substituted (C_{1-6})alkylOCONH, (C_{3-7})cycloalkylOCONH, (C_{3-7})cycloalkyl(C_{1-4})alkylOCONH, aryl(C_{1-4})alkylOCONH, heteroaryl(C_{1-4})alkylOCONH, (C_{1-4})alkylCONH, (C_{3-7})cycloalkylCONH, heteroarylCONH, arylCONH, aryl(C_{1-4}) alkylCONH or heteroaryl(C_{1-4})alkylCONH group,

U is (C_{1-3})alkylenoxy, (C_{1-3})alkylen, NR_g or an aromatic or heteroaromatic ring, optionally substituted with halogen, (C_{1-4})alkoxy, hydroxyl or (C_{1-4})alkyl, whereby Z and V are in ortho or meta position to each other, wherein R_g is hydrogen or (C_{1-4})alkyl,

V is a CHCH, $CH_2CH(OH)$, $CH(OH)CH_2$, CH_2CH_2, or CR_hR_iCH group, wherein R_h and R_i, independently, are hydrogen or (C_{1-4})alkyl,

W is (C_{1-2})alkylen, $CHCH_3$, O, S, SO_2, CO, COO, OCO, NR_fCO, $CONR_f$ or NR_f, wherein R_f is hydrogen or (C_{1-4})alkyl,

X is an optionally substituted (C_{1-4})alkylidene, (C_{1-4})alkylene, (C_{3-7})cycloalkylene, piperidin-diyl, pyrrolidin-diyl, benzothiazole-4,6-diyl, benzoxazole-4,6-diyl, 1H-benzotriazole-4,6-diyl, imidazo[1,2-a]pyridine-6,8-diyl, benzo[1,2,5]oxadiazole-4,6-diyl, benzo[1,2,5]thiadiazole-4,6-diyl, 1H-indole-5,7-diyl, 1H-indole-4,6-diyl, 1H-benzoimidazole-4,6-diyl or 1H-indazole-1,6-diyl, or X is an optionally substituted aromatic or heteroaromatic ring, whereby Y and $CONR_2$ are in meta position to each other

Y is a bond, oxygen, SO_2, SO_2NR_g, NR_g, CR_gOH, $CONR_g$ or NR_gCO group,

Z is oxygen, CH_2 or a bond, and

n is 0 to 3,

the number of atoms included in the macrocyclic ring being 14 to 17,

in free base or acid addition salt form.

The number of atoms included in the macrocyclic ring is 14 to 17.

Halogen denotes fluorine, bromine, chlorine or iodine.

Optional substituents on alkyl, alkoxy and cycloalkyl groups, or when R_a and R_b or R_c and R_d together with the nitrogen to which they are attached form a substituted pyrrolidinyl, piperidino, morpholino or piperazinyl group, may be one to three groups independently selected from hydroxy, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkoxy, (C_{1-4})alkylsulfanyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, (C_{1-4})sulfonyl, cyano, oxo, and hetero (C_{3-7})cycloalkyl.

Optional substituents on benzothiazole-4,6-diyl, benzooxazole-4,6-diyl, 1H-benzotriazole-4,6-diyl, imidazo[1,2-a]pyridine-6,8-diyl, benzo[1,2,5]oxadiazole-4,6-diyl, benzo[1,2,5]thiadiazole-4,6-diyl, 1H-indole-5,7-diyl, 1H-indole-4,6-diyl, 1H-benzoimidazole-4,6-diyl, 1H-indazole-1,6-diyl, aromatic or heteroaromatics rings are one to three groups independently selected from hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, SO_2(C_{1-4})alkyl, cyano, nitro, trifluoromethyl, halogen and optionally substituted carbamoyl.

When R_c and/or R_d is substituted aryl or heteroaryl, optional substituents may further be one to three groups selected from benzyloxy, phenoxy, SO_2NH_2, $NHSO_2$(C_{1-3})alkyl, carboxy, (C_{1-4})alkyloxycarbonyl, (C_{1-4})alkylcarbamoyl, (C_{1-4})alkylsulfonyl, (C_{1-4}) alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, hydroxy(C_{1-4})alkyl, phenyl, pyridinyl and optionally substituted amino.

Optional substituents on alkylidene, alkylene, cycloalkylidene, cycloalkylene, piperidin-diyl or pyrrolidin-diyl may be one to three groups independently selected from hydroxy, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkoxy, (C_{1-4})alkylsulfanyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, (C_{1-4}) sulfonyl, cyano, oxo, carboxy, carbamoyl and hetero (C_{3-7})cycloalkyl.

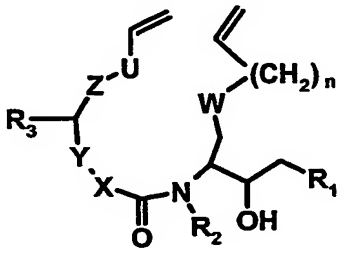
Optional substituents on amino groups can be one or two groups selected from (C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkyloxycarbonyl, aryl(C_{1-4})alkyloxycarbonyl, heteroaryl(C_{1-4})alkyloxycarbonyl.

Optional substituents on carbamoyl can be one or two groups selected from (C_{1-4})alkyl and (C_{1-4})alkoxy(C_{1-4})alkyl.

Heteroaryl is an aromatic 5- or 6- membered ring in which 1, 2 or 3 atoms are heteroatoms independently selected from O, N and S.

Any alkyl or alkoxy group is straight or branched.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the steps of cyclisation by metathesis of a compound of formula II



II

wherein R_1, R_2, R_3, U, W,X, Y, Z, and n are as defined above in the presence of a catalyst, for instance a ruthenium, tungsten or molybdenum complex, followed by an optional further reduction, oxidation or functionalisation of the resulting double bond, and recovering the so obtained compound of formula I in free base or acid addition salt form.

The reaction can be effected according to known methods, for example as described in Example 1.

Working-up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

The starting material of formula II may be produced for example as described in Example 1.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

The agents of the invention are inhibitors of aspartic proteases and can be used for the treatment of disorders involving processing by such enzymes. Particularly they inhibit beta-secretase and as such inhibit the generation of beta-amyloid and the subsequent aggregation into oligomers and fibrils.

The agents of the invention are therefore useful e.g. for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

Some of the agents of the invention also inhibit BACE2 (beta-site APP-cleaving enzyme 2) or Cathepsin D, close homologues of beta-secretase. Due to the correlation of BACE2 and CathD expression with a more tumorigenic and metastatic potential of tumor cells, such inhibitors are useful for the suppression of the metastasis process associated with tumor cells.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 10 to about 2000, preferably from about 10 to about 200 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 1 to about 1000, preferably from about 1 to about 500 mg of an agent of the invention.

The agents of the invention can be administered alone or in combination with other pharmaceutical agents effective, in the treatment of conditions mentioned above.

The pharmaceutical combination may be in form of a unit dosage form, whereby each unit dosage will comprise a predetermined amount of the two components, in admixture with suitable pharmaceutical carriers or diluents. Alternatively, the combination may be in form of a package containing the two components separately, e.g. a pack or dispenser-device adapted for the concomitant or separate administration of the two active agents, wherein these agents are separately arranged.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

In still a further aspect the present invention provides a method for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Abbreviations:

aq.	aqueous
BOC	tert-butoxycarbonyl
CDCl3	deuterated chloroform
conc.	concentrated
DCM	dichloromethane
DMPU	N, N'-dimethylpropylene urea
d6-DMSO	deuterated dimethylsulfoxide
EDC.HCl	1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
ES	electron spray
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hour
HCl	hydrochloric acid
HMDS	1,1,1,3,3,3-hexamethyl-disilazane
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
LC	liquid chromatography
LHMDS	lithium hexamethyldisilazide
MeCN	acetonitrile
min	minute
Mp	melting point
MS	mass spectroscopy
PL-CHO	polymer supported benzaldehyde (3 mmol/g)
PPTS	pyridinium-*para*-toluenesulfonate
Rf	retention factor (thin layer chromatography)
rt	room temperature
TBME	tert-butyl methyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example 1: 16(R/S)-[1(R/S)-Hydroxy-2-(3-methyl-benzylamino)-ethyl]-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione

3(S),4,14(R)-Trimethyl-16(R/S)-oxiranyl-1,4-diaza-cyclohexadecane-2,5-dione (67 mg, 0.2 mmol) is dissolved in 3-methyl-benzylamine (0.76 mmol, 3.8 eq) and the solution heated to 65 °C for 2 h. DCM (5 ml), PL-CHO (961 mg, 2.88 mmol) and 1 drop of glacial acetic acid are added and the mixture is shaken at rt for 4 h. The resin is filtered off and the filtrate evaporated. Purification of the residue by preparative thin layer chromatography or HPLC gives a thick brownish oil.

Rf: (DCM/methanol/acetic acid = 90/9/1): 0.36

MS (EI+): 460.0 [M+H]

The starting materials can be prepared as described hereafter:

a) 8,8-Dimethoxy-2,6(R)-dimethyloct-2-ene

A solution of 3,7(R)-dimethyl-oct-6-enal (R-Citronellal; 18.39 g, 119.2 mmol), trimethyl orthoformate (30.1 ml, 29.2 g, 275 mmol, 2.3 eq), ammonium nitrate (315 mg, 3.93 mmol, 0.033 eq) and PPTS (180 mg, 0.715 mmol, 0.006 eq) in 60 ml methanol is stirred at rt for 17 h. The mixture is poured on a saturated solution of sodium bicarbonate (300 ml) and extracted with diethylether (2 × 300 ml). The combined organic extracts are dried with sodium sulfate and the solvent evaporated. The desired product is obtained as a pale yellow oil (23.8 g) and used for the next step without further purification.

Rf: (n-hexane/diethylether = 90/10): 0.36

^{1}H-NMR (400 MHz, $CDCl_3$): 5.11 (t, 1H), 4.48 (t, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 2.08-1.92 (m, 2H), 1.70 (s, 3H), 1.69-1.55 (m, 2H), 1.60 (s, 3H), 1.43-1.31 (m, 2H), 1.14-1.27 (m, 1H), 0.93 (d, 3H).

b) 6,6-Dimethoxy-4(R)-methyl-hexanal

A mixture of 8,8-dimethoxy-2,6(R)-dimethyloct-2-ene (17.7 g, 88.2 mmol) and sodium bicarbonate (3.7 g, 44.1 mmol, 0.5 eq) in DCM/methanol = 80/20 (265 ml) is cooled to -78 °C and ozone is bubbled through the mixture. After 1 h 20 min the pale yellow solution turns pale blue and triphenylphosphine (34.8 g, 132 mmol) is added at -78 °C. The mixture is warmed to rt and stirred for 30 min. The solvent is evaporated and the residue taken up in n-hexane (176 ml), then stirred for 30 min. The precipitated triphenylphosphine oxide is removed by filtration and the solvent evaporated. The desired product is obtained as a pale yellow oil (28.9 g) and used for the next step without further purification.

Rf: (n-hexane/diethylether = 70/30): 0.24

c) 7,7-Dimethoxy-5(R)-methyl-hept-1-ene

To a suspension of methyltriphenylphosphonium bromide (1.96 g, 5.5 mmol, 1.1 eq) in THF (5 ml) is added potassium tert-butoxide (617 mg, 5.5 mmol, 1.1 eq) at 0 °C. The mixture is warmed to rt, stirred for 15 min at rt and cooled to 0 °C again and treated dropwise at 0°C with 6,6-dimethoxy-4(R)-methyl-hexanal (1.59 g, 5 mmol) in THF (2.5 ml, then warmed to rt and stirred for 2 h. The reaction mixture is poured onto ice-water (15 ml) and extracted with diethylether (3 × 15 ml). The combined organic extracts are dried with sodium sulfate and

the solvent evaporated. The residue is taken up in n-hexane (10 ml) and stirred for 30 min. The precipitated triphenylphosphine oxide is filtered off and the filtrate is directly poured on a chromatography column. Purification by chromatography on silica gel (n-hexane/diethylether 95/5) gives the desired product as a colorless oil (782 mg).
Rf: (n-hexane/diethylether = 70/30): 0.36
^{1}H-NMR (400 MHz, $CDCl_3$): 5.74-5.60 (m, 1H), 4.89 (d, 1H), 4.82 (d, 1H), 4.35 (t, 1H), 3.20 (1, 3H), 3.18 (s, 3H), 2.05-1.85 (m, 2H), 1.58-1.41 (m, 2H), 1.36-1.21 (m, 2H), 1.19-1.05 (m, 1H), 0.79 (d, 3H).

d) 3(R)-Methyl-hept-6-enal

To a solution of 7,7-Dimethoxy-5(R)-methyl-hept-1-ene (9.06 g, 52.6 mmol) in chloroform (53 ml) is added TFA / water = 50 / 50 (26.3 ml) at 0 °C, and the mixture is stirred at 8 °C for 17 h. The reaction mixture is cooled to 0 °C again and the pH adjusted to ca. 8.5 by addition of sodium bicarbonate (15.5 g, 184 mmol). After addition of water (210 ml) the mixture is extracted with DCM (2 × 210 ml). The combined organic extracts are washed with water (210 ml), dried with sodium sulfate and evaporated. The desired product is obtained as a volatile pale yellow oil (7.34 g) and used for the next step without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$): 9.77 (t, 1H), 5.88-5.73 (m, 1H), 5.09-4.93 (m, 2H), 2.44 (dd, 1H), 2.30-2.22 (m, 1H), 2.19-2.01 (m, 3H), 1.52-1.29 (m, 2H), 0.99 (d, 3H).

e) 2(R/S)-Amino-4(R)-methyl-oct-7-enenitrile

A solution of ammonium chloride (6.22 g, 116.3 mmol, 2.21 eq) and sodium cyanide (5.58 g, 85.7 mmol, 1.63 eq) in conc. aq. ammonium hydroxide (36.8 ml) and methanol (21 ml) is cooled to 0 °C and ammonia is bubbled through for 10 min. To this solution 3(R)-methyl-hept-6-enal (7.34 g, 52.6 mmol) in methanol (52.6 ml) is added at 0 °C. The mixture is warmed to rt and is stirred at rt for 2 days. Excess ammonia is evaporated, the mixture cooled to 0 °C and acidified by addition of 0.5 M HCl (105 ml). The mixture is washed with diethylether (2 × 105 ml) and the combined diethylether layers backwashed with 0.5 M HCl (105 ml). The acidic aqueous layers are combined, the pH adjusted to 8 by addition of 6 M aq. ammonium hydroxide and extracted with DCM (2 ×210 ml). The combined DCM layers are backwashed with water (210 ml), dried with sodium sulfate and evaporated to yield the desired product as a brownish oil (5.62 g, about 1:1 mixture of diastereomers), which is used for the next step without further purification.
Rf: (DCM/methanol = 98/2): 0.29,

MS (EI+): 153.1 [M+H],
1H-NMR (400 MHz, d6-DMSO): 5.84-5.70 (m, 1H), 4.98 (d, 1H), 4.90 (d, 1H), 5.67 (br d, 1H), 2.24 (br s, 2H), 2.12-1.90 (m, 2H), 1.70-1.53 (m, 2H), 1.48-1.32 (m, 2H), 1.27-1.12 (m, 2H), 0.91-0.83 (m, 3H).

f) [1(S)-(1(R/S)-Cyano-3(R)-methyl-hept-6-enylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butylester

To a solution of BOC-N-methyl-(L)-alanine (5.01 g, 24.64 mmol, 1.1 eq) and HOBt (4.95 g, 31.36 mmol, 1.4 eq) in DCM (112 ml) is added EDC (5.15 g, 26.88 mmol, 1.2 eq) at 0 °C. then after 10 min 2(R/S)-amino-4(R)-methyl-oct-7-enenitrile (3.41 g, 22.4 mmol). The mixture is allowed to warm to rt and stirring is continued at rt for 17 h. The reaction mixture is then cooled to 0 °C, 0.5 M HCl (224 ml) is added and the layers are separated. The aqueous phase is extracted with DCM/ethanol = 80/20 (2 × 224 ml), the combined organic layers are washed with 1 M potassium bicarbonate (224 ml), water (224 ml), dried with sodium sulfate and evaporated to yield the desired product as a yellowish oil (7.85 g, about 1/1 mixture of diastereomers), which is used for the next step without further purification.
Rf: (DCM/methanol = 95/5): 0.66,
MS (EI+): 360.4 [M+Na],
^{1}H-NMR (400 MHz, d6-DMSO, 2 diastereomers): 8.58 (d, 0.5H), 8.51 (d, 0.5H), 5.82-5.71 (m, 1H), 5.04-4.91 (m, 2H), 4.79-4.71 (m, 1H), 4.55-4.45 (br m, 0.5H), 4.32-4.15 (br m, 0.5H), 2.78 (s, 1.5H), 2.75 (s, 1.5H), 2.12-1.94 (m, 2H), 1.91-1.79 (m, 1H), 1.65-1.14 (m, 5H), 1.39 (s, 9H), 1.25 (br d, 3H), 0.89 (d, 1.5H), 0.85 (m, 1.5H).

g) 4(R)-Methyl-2(R/S)-(2(S)-methylamino-propionylamino)-oct-7-enoic acid methylester

To a solution of [1(S)-(1(R/S)-cyano-3(R)-methyl-hept-6-enylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butylester (7.84 g, 22.4 mmol) in methanol (67 ml) is added slowly 6.5 M HCl in Et_2O (138 ml, 896 mmol, 40 eq) at 0 °C. The mixture is allowed to warm to rt and is stirred at rt for 1 h. Water is added at 0 °C, the mixture is allowed to warm to rt and stirring is continued at rt for 30 min. The pH of the reaction mixture is adjusted to pH 8 by addition of potassium bicarbonate (89.7 g, 896 mmol) at 0 °C. The mixture is extracted with DCM (3 × 224 ml), the combined organic layers are dried with sodium sulfate and evaporated. The desired product is obtained as a brownish oil (5.04 g, about 1/1 mixture of diastereomers) and used for the next step without further purification.
Rf: (DCM/methanol = 95/5): 0.22,

MS (EI+): 271.0 [M+H],
^{1}H-NMR (400 MHz, d6-DMSO, 2 diastereomers): 8.08 (d, 0.5H), 8.02 (d, 0.5H), 5.81-5.68 (m, 1H), 5.02-4.88 (m, 2H), 4.42-4.38 (m, 1H), 3.62 (s, 1.5H), 3.61 (s, 1.5H), 2.99-2.89 (m, 1H), 2.19 (s, 1.5H), 2.18 (s, 1.5H), 2.11-1.89 (m, 3H), 1.75-1.61 (m, 1H), 1.58-1.12 (m, 4H), 1.10 (d, 1.5H), 1.08 (d, 1.5H), 0.88 (d, 1.5H), 0.84 (d, 1.5H).

h) 2(R/S)-[2(S)-(Hept-6-enoyl-methyl-amino)-propionylamino]-4(R)-methyl-oct-7-enoic acid methylester

EDC (4.29 g, 22.37 mmol, 1.2 eq) is added to a solution of 6-heptenoic acid (2.63 g, 20.5 mmol, 1.1 eq) and HOBt (4.12 g, 26.1 mmol, 1.4 eq) in DCM (93 ml) at 0 °C, followed after 10 min by 4(R)-methyl-2(R/S)-(2(S)-methylamino-propionylamino)-oct-7-enoic acid methylester (5.04 g, 18.64 mmol). The mixture is allowed to warm to rt and stirring is continued at rt for 3 days. The reaction mixture is then cooled to 0 °C and 0.5 M HCl (186 ml) is added and the layers separated. The aqueous phase is extracted with DCM/ethanol 8:2 (2 × 186 ml), the combined organic layers are washed with 1 M potassium bicarbonate (186 ml), water (186 ml), dried with sodium sulfate and evaporated. Purification by chromatography on silica gel (DCM/methanol 98/2) gives the desired product as a brownish oil (5.82 g, approx. 1:1 mixture of diastereomers).
Rf: (DCM/methanol = 95/5): 0.73,
MS (EI+): 403.3 [M+Na],
^{1}H-NMR (400 MHz, d6-DMSO): 8.09-8.00 (m, 1H), 5.83-5.68 (m, 2H), 5.04-4.89 (m, 4H), 4.37-4.26 (m, 1H), 3.61 (s, 1.5H), 3.60 (s, 1.5H), 2.85-2.69 (m, 3H), 2.34-2.23 (m, 2H), 2.09-1.93 (m, 4H), 1.75-1.60 (m, 1H), 1.55-1.08 (m, 7H), 1.18 (d, 3H), 0.89-0.79 (m, 3H).

i) Hept-6-enoic acid {1(S)-[1(R/S)-(2-chloro-acetyl)-3(R)-methyl-hept-6-enylcarbamoyl]-ethyl}-methyl-amide

Chloroiodomethane (1.45 ml, 3.51 g, 20 mmol, 4.0 eq) is added to a solution of 2(R/S)-[2(S)-(hept-6-enoyl-methyl-amino)-propionylamino]-4(R)-methyl-oct-7-enoic acid methylester (1.9 g, 5.0 mmol) in THF (37.5 ml) under an argon atmosphere, at -78 °C. LDA (1.57 M, 15.9 ml, 25 mmol, 5 eq) is added dropwise while the temperature of the reaction mixture is maintained below -68 °C, and the mixture is stirred for an additional 30 min. Glacial acetic acid (7.46 ml, 130 mmol) is then added dropwise while the temperature is maintained below -65 °C, stirring is continued for 15 min at -78 °C then the mixture is allowed to warm to 0 °C and a half-saturated aqueous sodium chloride solution is added (75 ml). The mixture is

extracted with TBME (2 × 75 ml), the combined organic layers are washed with 1 M sodium bicarbonate (75 ml), 1 M sodium sulfite (75 ml) and water (75 ml), dried with sodium sulfate and evaporated. The desired product, a brownish oil (3.15 g, about 1/1 mixture of diastereomers), is used for the next step without further purification.
Rf: (cyclohexane/EtOAc = 50/50): 0.45,
MS (LC/MS): 420.9/422.9 [M+Na].

j) Hept-6-enoic acid {1(S)-[1(R/S)-(2-chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enylcarbamoyl]-ethyl}-methyl-amide

A solution of hept-6-enoic acid {1(S)-[1(R/S)-(2-chloro-acetyl)-3(R)-methyl-hept-6-enylcarbamoyl]-ethyl}-methyl-amide (3.15 g, 5 mmol) in ethanol (110 ml) is added to a suspension of sodium borohydride (378 mg, 10 mmol, 2 eq) in ethanol (30 ml) at -78 °C. The temperature is kept below -75 °C during the addition and the mixture is stirred for an additional hour. 1 M HCl (25 ml) is added at -78 °C and the mixture is allowed to warm to rt. After evaporation of the ethanol, 1 M HCl (50 ml) is added and the mixture extracted with EtOAc (2 × 50 ml). The combined organic layers are washed with 1 M HCl (50 ml) and a half-saturated aqueous sodium chloride solution, dried with sodium sulfate and evaporated. Purification by chromatography on silica gel (cyclohexane/EtOAc 70/30 to 50/50) gives the desired product as a brown oil (1.38 g, approx. 1:1 mixture of diastereomers).
Rf: (cyclohexane/EtOAc = 50/50): 0.30,
MS (LC/MS): 400.9/402.9 [M+H], 422.9/424.9 [M+Na].

k) 16(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadec-10-ene-2,5-dione

A solution of hept-6-enoic acid {1(S)-[1(R/S)-(2-chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enylcarbamoyl]-ethyl}-methyl-amide (1.38 g, 3.44 mmol) in DCM (17.2 ml) is added dropwise within an hour to a refluxing solution of [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs II catalyst, 146 mg) in DCM (344 ml), under an argon atmosphere. The mixture is refluxed for an additional hour and the solvent evaporated. The residue is purified by chromatography on silica gel (DCM/methanol 95/5), giving the desired product as a brownish foam (1.24 g, approx. 1:1 mixture of diastereomers).
Rf: (DCM/methanol = 95/5): 0.39.

l) 16(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione

16(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadec-10-ene-2,5-dione (1.24g, 3.32mmol) is hydrogenated at rt (1 atm H_2) in ethanol (33 ml) with Pd/C (10% Engelhard 4505, 332 mg) for 1h. More catalyst is added (332 mg) and the hydrogenation is continued for 4 h. The catalyst is filtered off and the filtrate evaporated. The residue is purified by chromatography on silica gel (DCM/methanol 95/5) and gives the desired product as a brownish foam (869 mg, about 1/1 mixture of diastereomers).
Rf: (DCM/methanol = 95/5): 0.40,
MS (LC/MS): 375.0/377.0 [M+H], 396.9/398.9 [M+Na].

m) 3(S),4,14(R)-Trimethyl-16(R/S)-oxiranyl-1,4-diaza-cyclohexadecane-2,5-dione

To a solution of 16(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione (718 mg, 1.91 mmol) in THF (3.8 ml) is added 1 M NaOH (2.3 ml, 2.3 mmol, 1.2 eq) dropwise at 0 °C and the reaction mixture is stirred for 2 h at 0 °C. Water is added (19 ml) and the mixture is extracted with DCM (2× 19 ml), the combined organic layers are washed with saturated ammonium chloride (19 ml) and saturated sodium chloride (19 ml), dried with sodium sulfate and evaporated to give the product as a brownish oil (654 mg, approx. 1:1 mixture of diastereomers).
Rf: (DCM/methanol = 95/5): 0.52,
MS (EI+): 339.3 [M+H], 361.3 [M+Na].

The following compounds are obtained by a similar procedure:

Example 1a: 16(R/S)-[1(R/S)-Hydroxy-2-(3-methoxy-benzylamino)-ethyl]-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione

Rf: (DCM/methanol 95:5): 0.33
MS (LC/MS): 476.0 [M+H]

Example 1b: 16(R/S)-[1(R/S)-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione

Rf: (DCM/methanol 9:1): 0.44,
MS (LC/MS): 488.0 [M+H].

Example 1c: **16(R/S)-[1(R/S)-Hydroxy-2-(2-pyridin-4-yl-ethylamino)-ethyl]-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione**
Rf: (DCM/methanol/NH_3 = 90:10:1): 0.25
MS (LC/MS): 461.0 [M+H].

Example 1d: **16(R/S)-{2-[2-(3,4-Dimethoxy-phenyl)-ethylamino]-1(R/S)-hydroxy-ethyl}-3(S),4,14(R)-trimethyl-1,4-diaza-cyclohexadecane-2,5-dione**
Rf: (DCM/methanol/NH_3 90:9:1): 0.30
MS (LC/MS): 520.0 [M+H].

Example 2: **[(3S,6S,14R,16S)-16-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-6-yl]-carbamic acid tert-butyl ester**
199 mg (0.35 mmol) [(E)-(3S,6S,14R,16S)-16-((1S,3R)-3-butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-10-en-6-yl]-carbamic acid tert-butyl ester were stirred with 20 mg 10% Pd-C in 10 ml THF and 10 ml EtOH under an hydrogen atmosphere for 1 h. The mixture was filtered over a pad of celite and the solvent evaporated.
Yield: 181 mg of the title compound as a white powder.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.28 min; MS(ES) $M+Na^+$=591.

The starting materials can be prepared as described hereafter:

a) [(3S,6S,14R,16S)-16-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-10-en-6-yl]-carbamic acid tert-butyl ester
183 mg (0.37 mmol) [(3S,6S,14R,16S)-3,14-dimethyl-16-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,5-dioxo-1,4diaza-cyclohexadec-10-en-6-yl]-carbamic acid tert-butyl ester were dissolved in 1.5 mL (excess) butylamine and heated to 65°C under nitrogen for two hours. The reaction mixture was evaporated, the residue taken up in toluene and evaporated to dryness to yield 199 mg of the title compound.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.00 min; MS(ES) MNa^+=589

b) [(3S,6S,14R,16S)-3,14-Dimethyl-16-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,5-dioxo-1,4diaza-cyclohexadec-10-en-6-yl]-carbamic acid tert-butyl ester

To a refluxing solution of 6 mg tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV)dichloride in 300 ml DCM under a nitrogen atmosphere were slowly added 210 mg (0.402 mmol) ((S)-1-{(S)-1-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarbamoyl]-ethylcarbamoyl}-hex-5-enyl)-carbamic acid tert-butyl ester in 50 ml degassed DCM. After 3 h the mixture was cooled to rt and purified via chromatography on silica gel (EtOAc/hexane 1:1) to yield 183 mg of [(3S,6S,14R,16S)-3,14-dimethyl-16-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,5-dioxo-1,4diaza-cyclohexadec-10-en-6-yl]-carbamic acid tert-butyl ester as a solid (5:1 mixture of double bond isomers).

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.19 min; MS(ES) MNa^+=516

c) ((S)-1-{(S)-1-[(1S,3R)-3-Methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarbamoyl]-ethylcarbamoyl}-hex-5-enyl)-carbamic acid tert-butyl ester

194 mg (0.489 mmol) of a {(S)-1-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester in 2 ml 4N HCl in dioxan was kept 3 h at rt and concentrated in vacuo. The residue was taken up in 3 ml DCM and treated with 187 mg (0.734 mmol) (2S)-*tert*-butoxycarbonyl-2-amino-6-heptenoic acid, 79 mg (0.516 mmol) $HOBt.H_2O$, 140 mg (0.734 mmol) EDC.HCl and 0.27 ml (1.95 mmol) Et_3N and stirred overnight. The mixture was diluted with EtOAc and washed successively with water, 5% aqueous citric acid, water, 5% aqueous $NaHCO_3$ and water (4x). Evaporation of the mixture and chromatography on silica gel (EtOAc/hexane 1:2 and 1:1) gave 255 mg ((S)-1-{(S)-1-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarbamoyl]-ethylcarbamoyl}-hex-5-enyl)-carbamic acid tert-butyl ester.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.94 min; MS(ES) MNa^+=544

d) {(S)-1-[(1S,3R)-3-Methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester

1.0 g (3.08 mmol) of a 1:1 mixture of [(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester *and* [(1R,3R)-3-methyl-1-

((2R,4S)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester in 6 ml 4N HCl in dioxan was kept 3 h at rt and concentrated in vacuo. The residue was taken up in 10 ml DCM and treated with 582 mg (3.08 mmol) Boc-Ala-OH, 499 mg (3.26 mmol) $HOBt.H_2O$, 882 mg (4.62 mmol) EDC.HCl and 1.72 ml (12.3 mmol) Et_3N and stirred overnight. The mixture was diluted with EtOAc and washed successively with water, 5% aqueous citric acid, water, 5% aqueous $NaHCO_3$ and water (4x). Evaporation of the mixture and chromatography on silica gel (EtOAc/hexane 1:7, 1:6 and 1:3) gave 524 mg of a faster eluating diastereomer and 592 mg of {(S)-1-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enylcarba-moyl]-ethyl}-carbamic acid tert-butyl ester as a colorless oil.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.29 min; MS(ES) MNa^+=419

e) [(1S,3R)-3-Methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester *and* **[(1R,3R)-3-methyl-1-((2R,4S)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester**

At -78°C under nitrogen atmosphere a solution of 3.8 g (12.2 mmol) of a 1:1 mixture of [(1S,3R)-3-Methyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3-Methyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester and 2.2 ml (18.3 mmol) DMPU in 50 ml THF were treated with 67.8 ml (25.6 mmol) of a 0.41 M solution of LHMDS in THF. After 50 min 1.30 ml (20.7 mmol) methyl iodide were added in one portion. Then after 45 min the reaction was quenched with 4.56 ml (61 mmol) propionic acid and the mixture was allowed to warm to rt and diluted with EtOAc and water. The organic phase was washed successively with 5% aqueous citric acid, water, 5% aqueous NaHCO3 and water (4x). Evaporation of the mixture and chromatography on silica gel (EtOAc/hexane 1:6) gave 4.27 g of a 1:1 mixture of [(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3-methyl-1-((2R,4S)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester as a colorless oil that solidified upon standing. LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 6.04 min; MS(ES) MNa^+=348

f) [(1S,3R)-3-Methyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester *and* **[(1R,3R)-3-methyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester**

10.18 g (30 mmol) of a 1:1 mixture of [(1S,3R)-3,7-dimethyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3,7-Dimethyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester in a mixture 300 ml DCM and 100 ml MeOH was cooled to -75°C. After addition of 1.26 g (15 mmol) $NaHCO_3$ a stream of O_3 in O_2 was passed through the stirred mixture till a blue color persisted. The excess ozone was removed by flushing with O_2. After addition of 9.44 g (36 mmol) triphenylphosphine the mixture was allowed to warm up at rt and stirred for 4 h. The mixture was filtered and concentrated in vacuo. Chromatography on silica gel (EtOAc/Hexane 1:1) gave 11.1 gram of aldehyde contaminated with 20% triphenylphosphine oxide. After 1 h an under nitrogen gas stirred suspension of 11.8 g (33 mmol) methyl triphenylphosphonium bromide and 3.36 g (30 mmol) tBuOK in 150 ml toluene was cooled with an ice bath and treated with a solution of the abovementioned aldehyde in 70 ml THF. After 30 min the mixture was quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried with Na_2SO_4 and evaporated. Column chromatography of the residue on silica gel (EtOAc/hexane 1:5) gave 3.8 g of a 1:1 mixture of [(1S,3R)-3-Methyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3-Methyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester as a solidifying oil. LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.73 min; MS(ES) MNa^+=334

g) [(1S,3R)-3,7-Dimethyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester *and* **[(1R,3R)-3,7-dimethyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester**

To a solution of 20.2 g (60 mmol) of a 1:1 mixture of [(1S,3R)-3,7-dimethyl-1-((S)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3,7-dimethyl-1-((R)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester in 200 ml THF were added 2 g Raney nickel and stirred under an atmosphere of hydrogen. When the take up of hydrogen ceased the reaction mixture was filtered carefully (*Raney nickel is pyrophoric!*) via a pad of celite. Evaporation of the solvent gave 20.3 g of a 1:1 mixture of [(1S,3R)-3,7-dimethyl-1-((S)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl

ester and [(1R,3R)-3,7-dimethyl-1-((R)-5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester as a colorless oil.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 6.24 min; MS(ES) MNa^+=362

h) [(1S,3R)-3,7-Dimethyl-1-((S)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester *and* **[(1R,3R)-3,7-dimethyl-1-((R)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester**

Solution A was prepared as follows. A solution of 20.67 g (128 mmol) HMDS in 200 ml dry THF under nitrogen atmosphere was cooled at -70°C and 80 ml of a 1.6 M solution of BuLi in hexane (128 mmol) were added dropwise. After 10 min a solution of 10.75 g (128 mmol) 5H-furan-2-one in 10 ml dry THF was added dropwise. The solution A was kept at -40°C to prevent the formation of a ,precipitate and was added to a stirred solution of 50.1 g (122 mmol) [(R)-3,7-dimethyl-1-(toluene-4-sulfonyl)-oct-6-enyl]-carbamic acid tert-butyl ester in 300 ml dry THF at -70°C. After stirring the mixture at this temperature for 1 h the mixture was poored directly in 500 ml water and 500 ml EtOAc. The organic phase was washed successively with 5% aqueous citric acid, water (2x), 5% aqueous NaHCO3 solution and water (4x). The reaction mixture was evaporated and the residue chromatographed over silica gel (EtOAc/hexane 1:5) to yield 26.2 g of a 1:1 mixture of [(1S,3R)-3,7-dimethyl-1-((S)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester and [(1R,3R)-3,7-dimethyl-1-((R)-5-oxo-2,5-dihydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester as a colorless oil that solidified upon standing.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 65-100% MeCN (6 min), 100% MeCN (1.5 min)): 2.99 min; MS(ES) MNa^+=360

i) [(R)-3,7-Dimethyl-1-(toluene-4-sulfonyl)-oct-6-enyl]-carbamic acid tert-butyl ester

21.34 G (131.4 mmol) R-(+)-citronellal, 14.63 g (125 mmol) carbamic acid tert-butyl ester, 24.6 g (138 mmol) sodium 4-methyl-benzenesulfinate and 7.5 ml (200 mmol) formic acid were stirred in 100 ml acetonitrile at rt for 4 days. The mixture was diluted with 300 ml EtOAc and 300 ml water. The organic phase was successively washed with 5% aqueous citric acid acid, water, 5% aqueous $NaHCO_3$ solution and four times with water. After addition of 10 ml EtOH the solution was concentrated in vacuo yielding 50.1 g of the title compound as a colorless oil that solidified upon standing.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 6.85 min; MS(ES) MNa^+=432

The following compounds are obtained by a similar procedure, using instead of (2S)-*tert*-butoxycarbonyl-2-amino-6-heptenoic acid in step c of Example 2 either hex-5-enoic acid, hept-6-enoic acid, oct-7-enoic acid, (S)-2-tert-butoxycarbonylamino-pent-4-enoic acid, pent-4-enoic acid, 3-allyloxy-propionic acid or allyloxy-acetic acid:

Example 2a: 2R,4S)-N-Butyl-4-((2S,5S,7R)-2,7-dimethyl-3,15-dioxo-1,4diaza-cyclopentadec-5-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.32 min; MS(ES) MNa^+= 462

Example 2b: (2R,4S)-N-Butyl-4-((2S,5S,7R)-2,7-dimethyl-3,16-dioxo-1,4diaza-cyclohexadec-5-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.68 min; MS(ES) MNa^+= 476

Example 2c: (2R,4S)-N-Butyl-4-((2S,5S,7R)-2,7-dimethyl-3,17-dioxo-1,4diaza-cycloheptadec-5-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.05 min; MS(ES) MNa^+= 490

Example 2d: [(3S,6S,12R,14S)-14-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,12-dimethyl-2,5-dioxo-1,4diaza-cyclotetradec-6-yl]-carbamic acid tert-butyl ester

LC/MS (Nucleosil C-18HD, 4x70 mm, 3μM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.70 min; MS(ES) MNa^+= 563

Example 2e: (2R,4S)-N-Butyl-4-((2S,5S,7R)-2,7-dimethyl-3,14-dioxo-1,4diaza-cyclotetradec-5-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.02 min; MS(ES) MNa^+= 448

Example 2f: (2R,4S)-N-Butyl-4-((6S,9S,11R)-6,11-dimethyl-4,7-dioxo-1-oxa-5,8-diaza-cyclohexadec-9-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.92 min; MS(ES) MNa^+= 478

Example 2g: (2R,4S)-N-Butyl-4-((5S,8S,10R)-5,10-dimethyl-3,6-dioxo-1-oxa-4,7-diaza-cyclopentadec-8-yl)-4-hydroxy-2-methyl-butyramide

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.11 min; MS(ES) MNa^+= 464

Example 2h: (2R,4S)-N-Butyl-4-hydroxy-2-methyl-4-((2S,5S,7R)-1,2,7-trimethyl-3,15-dioxo-1,4diaza-cyclopentadec-5-yl)-butyramide

The compound is prepared according to a similar procedure as example 2 except for using L-Boc-N-methylalanine in step d.

LCMS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.58 min; MS(ES) MNa^+= 476.4

Example 3: (2R,4S)-4-((2S,5S,7R,15S)-15-Acetylamino-2,7-dimethyl-3,16-dioxo-1,4-diaza-cyclohexadec-5-yl)-N-butyl-4-hydroxy-2-methyl-butyramide

45 mg (0.079 mmol) [(3S,6S,14R,16S)-16-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-6-yl]-carbamic acid tert-butyl ester are treated with 1 ml 4N HCl in dioxan for 1 h and then evaporated. The residue is taken up in 3 ml THF and 1 ml EtOH and, under ice cooling, treated with 1 ml 10% aqueous Na_2CO_3 and 0.112 ml (1.6 mmol) acetyl chloride. The mixture is stirred vigorously at rt for 1 h and concentrated. After stirring the residual product with water and TBME/hexan for 30 min the mixture is filtered to yield 23 mg of the title compound.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.06 min; MS(ES) MNa^+=533

Example 4: N-[(3S,6S,14R,16S)-16-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-6-yl]-isonicotinamide

45 mg (0.079 mmol) [(3S,6S,14R,16S)-16-((1S,3R)-3-Butylcarbamoyl-1-hydroxy-butyl)-3,14-dimethyl-2,5-dioxo-1,4diaza-cyclohexadec-6-yl]-carbamic acid tert-butyl ester are treated with 4 ml 4N HCl in dioxan for 1 h and then evaporated. The residue is taken up in 2 ml THF and 2 ml EtOH and treated subsequently with 14 mg (0.118 mmol) isonicotinic acid,13 mg (0.095 mmol) HOBt, 22 mg (0.118 mmol) EDCI and 0.055 ml (0.4 mmol) Et_3N. After 24 h the mixture is diluted with EtOAc, washed subsequently with water, 5% citric acid, water, sat. aq. $NaHCO_3$ soln. and water. The organic phase is evaporated, the residual solid is washed with EtOAc and filtered to yield 21 mg of the desired product as a white powder.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.69 min; MS(ES) MNa^+=596

Example 5: (2R,4S)-N-Butyl-4-((3S,6S,8R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclohexadec-6-yl)-4-hydroxy-2-methyl-butyramide

74 mg (0.15 mmol) (2R,4S)-N-Butyl-4-((E)-(3S,6S,8R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclohexadec-11-en-6-yl)-4-hydroxy-2-methyl-butyramide (example 6) are stirred with 20 mg 10% Pd-C in 5 ml MeOH in a hydrogen atmosphere for 1 h. The mixture is filtered over a pad of celite and the solvent evaporated. The residue is crystalized from toluene and gave 34 mg of the title compound as a white powder.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.88 min; MS(ES) MNa^+= 511

The starting materials can be prepared as described thereafter:

a) (2R,4S)-N-Butyl-4-((E)-(3S,6S,8R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclohexadec-11-en-6-yl)-4-hydroxy-2-methyl-butyramide

99 mg (0.21 mmol) (E)-(3S,6S,8R)-3,8-dimethyl-6-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-1,1-dioxo-1lambda*6*-thia-5-aza-cyclohexadec-11-en-4-one are dissolved in 1.5 mL (excess) butylamine and heated to 65°C under nitrogen for two hours. The reaction mixture is evaporated, the residue chromatographed on silica gel (EtOAc/hexane 1:1) to yield 74 mg of the title compound as a white solid.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.64 min; MS(ES) MNa^+= 509.

b) (E)-(3S,6S,8R)-3,8-Dimethyl-6-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-1,1-dioxo-1lambda*6*-thia-5-aza-cyclohexadec-11-en-4-one

100 mg (0.218 mmol) (S)-3-(Hex-5-ene-1-sulfonyl)-2-methyl-N-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-propionamide in 5 ml DCM are added slowly to a refluxing solution of 10 mg (0.01 mmol) tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV)dichloride in 200 ml DCM under nitrogen. After 2 h the mixture is passed through a pad of silica gel (EtOAc/hexane 1:1) to yield 99 mg of the title compound as a solid.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.87 min; MS(ES) MNa^+= 436

c) (S)-3-(Hex-5-ene-1-sulfonyl)-2-methyl-N-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-propionamide

162 mg (0.5 mmol) of a 1:1 mixture of [(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester *and* [(1R,3R)-3-methyl-1-((2R,4S)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester in 2 ml 4N HCl in dioxan was kept 3 h at rt and concentrated in vacuo. The residue is taken up in 10 ml DCM and treated with 157 mg (0.675 mmol) (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid, 91 mg (0.59 mmol) $HOBt.H_2O$, 129 mg (0.675 mmol) EDC.HCl and 0.383 ml (2.75 mmol) Et_3N and stirred overnight. The mixture is diluted with EtOAc and washed successively with water, 5% aqueous citric acid, water, 5% aqueous $NaHCO_3$ and water (4x). Evaporation of the mixture and chromatography on silica gel (EtOAc/hexane 1:3, 1:2 and 1:1) gave 50 mg of a faster eluting diastereomer and 56 mg of (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-N-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-propionamide.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.64 min; MS(ES) MNa^+=464

d) (S)-3-(Hex-5-ene-1-sulfonyl)-2-methyl-propionic acid

2.02 g (10 mmol) (S)-3-hex-5-enylsulfanyl-2-methyl-propionic acid in 20 ml MeOH and 10 ml water is cooled at +4°C and treated with 7.35 g (22 mmol) oxone® and allowed to warm to rt overnight. The mixture is diluted with 20 ml 1N HCl and extracted with EtOAc (3x). The combined organic phases are dried with Na_2SO_4, evaporated and crystallised from TBME/hexane to yield 1.6 g of the desired product as a white powder, mp 51-54°C.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.58 min; MS(ES) MNa^+= 257.

e) (S)-3-Hex-5-enylsulfanyl-2-methyl-propionic acid
1.62 g (10 mmol) (S)-3-Acetylsulfanyl-2-methyl-propionic acid in 20 ml MeOH is treated with 7.5 ml 4N NaOH and 1.63 g (10 mmol) 6-bromo-hex-1-ene and stirred for 1 h at rt. The mixture is diluted with 50 ml EtOAc and acidified with 25 ml 1N HCl. The organic phase is washed with brine (2x), dried with Na_2SO_4 and concentrated in vacuo to yield 2.05 g of (S)-3-hex-5-enylsulfanyl-2-methyl-propionic acid as an oil which is used without purification for the next step.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.03 min; MS(ES) $[MNa_2\text{-}H]^+$= 247.

Example 6: N-Butyl-4-((R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclopentadec-6-yl)-4-hydroxy-2-methyl-butyramide
The title compound can be obtained as a 1:1 mixture of two diastereomers similarly to Example 5, but using 2-methyl-3-(pent-4-ene-1-sulfonyl)-propionic acid instead of (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid in step c:
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.49 and 4.61 min (2 diastereomers); MS(ES) $[MNa_2\text{-}H]^+$= 497.2

The starting material can be prepared as described hereafter:

a) 2-Methyl-3-(pent-4-ene-1-sulfonyl)-propionic acid
0.743 g (6.2 mmol) racemic 3-mercapto-2-methyl-propionic acid in 5 ml EtOH was treated with 3.1 ml (12.4 mmol) 4N NaOH and 1.4 g (6.2 mmol) benzenesulfonic acid pent-4-enyl ester and stirred for 1 h at rt. The organic volatiles are evaporated and the mixture is washed with 10 ml TBME, acidified with 2 ml 4N HCl and extracted twice with EtOAc. The organic

phase is concentrated in vacuo. The residue is taken up in 10 ml water and 10 ml MeOH, cooled at +4°C and treated portionwise with 4.55 g (13.6 mmol) oxone® and allowed to warm to rt overnight. The mixture is diluted with 20 ml 1N HCl and extracted with EtOAc (3x). The combined organic phases are dried with Na_2SO_4, evaporated and chromatographed on silica gel (EtOAC/hexane/0-0.6%HOAC). The purified fraction is crystallised from TBME/hexane to yield 0.81 g desired product as a white powder.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.03 min; MS(ES) MNa^+= 243.0, $[MNa_2-H]^+$= 265.0

Example 7: (2R,4S)-N-Butyl-4-((3S,6S,8R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclotetradec-6-yl)-4-hydroxy-2-methyl-butyramide

The title compound can be obtained similarly to Example 5, but using 6-bromo-but-1-ene instead of 6-bromo-hex-1-ene in step e.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.25 min; MS(ES) MNa^+= 483.2

Example 8: (2R,4S)-N-Butyl-4-((3S,6S,8R)-3,8-dimethyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cycloheptadec-6-yl)-4-hydroxy-2-methyl-butyramide

The title compound can be obtained similarly to Example 5, but using benzenesulfonic acid hept-6-enyl ester instead of 6-bromo-hex-1-ene in step e.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.18 min; MS(ES) MNa^+= 525.4

The starting material can be prepared as described hereafter:

a) Benzenesulfonic acid hept-6-enyl ester

To a solution of 1 g (8.76 mmol) 6-hepten-1-ol, 1.41 ml 17.5 mmol) pyridine in 10 ml DCM at 4°C are added dropwise 1.12 ml (8.76 mmol) benzenesulfonyl chloride. The mixture is stirred overnight at rt and poured into water. The organic phase is washed subsequently with 5% aqueous citric acid, water and 5 % aqueous $NaHCO_3$, dried with Na_2SO_4 and evaporated. The residue is chromatographed on silica gel (EtOAc/hexan 5:1 and 3:1) to yield 1.93 g of benzenesulfonic acid hept-6-enyl ester.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.94 (d, 2H), 7.68 (t, 1H), 7.60 (t, 2H), 5.84-5.73 (m, 1H), 5.05-4.94 (m, 2H)), 4.07 (t, 2H), 2.07-1.97 (m, 2H), 1.73-1.65 (m, 2H), 2.66-2.59 (m, 3H), 1.40-1.30 (m, 4H)

Example 9: N-Butyl-4-hydroxy-2-methyl-4-((R)-7-methyl-1,1,3-trioxo-1lambda*6*-thia-4-aza-cyclohexadec-5-yl)-butyramide

The title compound is obtained similarly to Example 5, but using (hept-6-ene-1-sulfonyl)-acetic acid instead of (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid in step c.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.22 and 5.40 min (2 diastereomers); MS(ES) MNa^+= 497.2 and 497.2

The starting material is prepared similarly to (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid, starting from acetylsulfanyl-acetic acid and benzenesulfonic acid hept-6-enyl ester:

a) (hept-6-ene-1-sulfonyl)-acetic acid

^{1}H-NMR (400 MHz, $CDCl_3$): 5.90-5.79 (m, 1H), 5.08-4.94 (m, 2H)), 3.30 (s, 2H), 2.70 (t, 2H), 2.09 (m, 2H), 1.65 (m, 2H), 1.45 (m, 4H).

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.78 min; MS(ES) $[MNa_2\text{-}H]^+$= 233.0

Example 10: N-Butyl-4-hydroxy-2-methyl-4-((R)-8-methyl-1,1,4-trioxo-1lambda*6*-thia-5-aza-cyclohexadec-6-yl)-butyramide

The title compound is obtained similarly to Example 5, but using 3-(hex-5-ene-1-sulfonyl)-propionic acid instead of (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid in step c.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.71 and 4.83 min (1:1 diastereomeric mixture); MS(ES) MNa^+=497.2 and 497.2

The starting material is prepared similarly to (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid, but from 3-mercapto-propionic acid and 6-bromo-hex-1-ene:

a) 3-(Hex-5-ene-1-sulfonyl)-propionic acid

^{1}H-NMR (400 MHz, $CDCl_3$): 5.87-5.76 (m, 1H), 5.12-5.02 (m, 2H)), 3.35 (t, 2H), 3.10-3.02 (m, 2H), 2.99 (t, 2H), 2.17 (m, 2H), 1.92 (m, 2H), 1.60 (m, 2H).

Example 11: N-Butyl-4-hydroxy-2-methyl-4-((R)-9-methyl-1,1,5-trioxo-1lambda*6*-thia-6-aza-cyclohexadec-7-yl)-butyramide

The title compound is obtained similarly to Example 5, but using 4-(pent-4-ene-1-sulfonyl)-butyric acid instead of (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid in step c.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.25 and 4.34 min (1:1 diastereomeric mixture); MS(ES) MNa^+= 497.2

The starting material is prepared similarly to (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid, starting from thiobutyrolactone and benzenesulfonic acid pent-4-enyl ester:

a) 4-(pent-4-ene-1-sulfonyl)-butyric acid

1H-NMR (400 MHz, CDCl3): 5.82-5.69 (m, 1H), 5.15-5.05 (m, 2H)), 3.13-3.04 (m, 2H), 3.02-2.95 (m, 2H), 2.60 (t, 2H), 2.28-2.10 (m, 4H), 2.05-1.90 (m, 2H).

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 2.65 min; MS(ES) MNa^+= 243.0

Example 12: N-Butyl-4-hydroxy-4-((R)-16-methoxy-9-methyl-13-oxo-2,12,17-triaza-bicyclo[12.3.1]octadeca-1(17),14(18),15-trien-11-yl)-2-methyl-butyramide

A solution of 16-methoxy-9-methyl-11-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,12,17-triaza-bicyclo[12.3.1]octadeca-1(17),14(18),15-trien-13-one (49 mg, 0.12 mmol) in 1.2 ml (excess) butylamine is stirred at 50° for 3 h. Excess butylamine is evaporated and the residue purified by chromatography on silica gel to afford 7 mg of the title compound (two diastereomers) as a slightly yellow powder.

Mp 178-182°C.

HPLC (XTerra 4.5 cm, 95% CH_3CN, 50°C): 3.98 min. MS (LC/MS): 459.0 ($MH^+ - H_2O$), 477.3 (MH^+).

The starting material is prepared as follows:

a) 16-Methoxy-9-methyl-11-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,12,17-triaza-bicyclo[12.3.1]octadeca-1(17),14(18),15-trien-13-one

A solution of 60 mg (0.15 mmol) 16-methoxy-9-methyl-11-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,12,17-triaza-bicyclo[12.3.1]octadeca-1(17),5,14(18),15-tetraen-13-one in 2 ml MeOH is hydrogenated under 1 atm hydrogen in the presence of 9 mg Pd/C for 2h at rt. Filtration and evaporation afforded 49 mg of title compound as a brownish foam.

b) 16-Methoxy-9-methyl-11-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-2,12,17-triaza-bicyclo[12.3.1]octadeca-1(17),5,14(18),15-tetraen-13-one

A solution of 90 mg (0.21 mmol) 2-but-3-enylamino-6-methoxy-N-[3-methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-isonicotinamide in 6 ml DCM is added dropwise over 30 min to a refluxing solution of 3.5 mg tricyclohexylphosphine [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidene] ruthenium (IV) dichloride ('Grubbs second generation catalyst') in 6 ml DCM and then stirred for 1h at reflux. LC/MS showed that only little product had been formed, therefore 7 mg catalyst are added and the mixture stirred for 18 h at reflux. Again, 11 mg catalyst are added and heating continued for 4h. The reaction mixture is directly chromatographed on silica gel and eluted with DCM/MeOH 98:2 to afford 50 mg of the title compound (2 diastereomers) as a greenish foam.

HPLC (XTerra 4.5 cm, 95% CH_3CN, 50°C): 3.85 min and 4.45 min (diastereoisomers). MS (LC/MS): 402.4 (MH+).

c) 2-But-3-enylamino-6-methoxy-N-[3-methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-isonicotinamide

A solution of 155 mg (0.7 mmol) 2-but-3-enylamino-6-methoxy-isonicotinic acid, 105 mg (0.47 mmol) (R)-3-Methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-carbamic acid tert-butyl ester and 63 mg (0.42 mmol) HOBt.H_2O in 8 ml DMF is cooled to 0°, treated with 107 mg (0.56 mmol) EDC.HCl and stirred at rt for 3h. The reaction mixture is diluted with EtOAc and washed with 0.5 N aqueous citric acid, 2 M $KHCO_3$ and brine, then dried over Na_2SO_4, filtered and evaporated. Chromatography on silica gel afforded 90 mg desired product as a colourless oil.

HPLC (XTerra 4.5 cm, 95% CH_3CN, 50°C): 4.25 min. MS (LC/MS): 430.5 (MH^+).

d) 2-But-3-enylamino-6-methoxy-isonicotinic acid

A mixture of 1.0 g (5.3 mmol) 2-chloro-6-methoxy-isonicotinic acid, 4.4 g (53 mmol, 86% pure by NMR) but-3-enylamine and 85 mg (0.53 mmol) $CuSO_4$ in 10 ml H_2O is stirred in a pressurized reaction vessel for 36 h at 140°C. The reaction mixture is diluted with an 0.5 M aqueous citric acid and extracted two times with EtOAc. The combined extracts are washed with citric acid solution, water and brine, dried over Na_2SO_4, filtered and the solvent evaporated. Chromatography on silica gel afforded 2-but-3-enylamino-6-methoxy-isonicotinic acid (188 mg, 16%) as an off-white powder.
HPLC (XTerra 4.5 cm, 95% CH_3CN, 50°C): 3.64 min. MS (LC/MS): 223.3 (MH^+).

The following compounds are obtained by a similar procedure:

Example 13: N-Butyl-4-((R)-6,12-dimethyl-2,13-dioxo-3,12-diaza-bicyclo[12.3.1]octa deca-1(18),14,16-trien-4-yl)-4-hydroxy-2-methyl-butyramide
The title compound is obtained similarly to Example 12 as a 1:1 mixture of diastereomers, using N-allyl-N-methyl-isophthalamic acid instead of 2-but-3-enylamino-6-methoxy-isonicotinic acid in step c.
LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.35 min; MS(ES) MNa^+= 496.4

The starting material is prepared as follows:

a) N-Allyl-N-methyl-isophthalamic acid
A solution of 2.5 g (13.9 mmol) isophthalic acid monomethyl ester in 25 ml THF, cooled at -30 °C is treated with 2.32 ml (16.9 mmol) Et_3N followed by 2.0 ml (15.3 mmol) isobutyl chloroformate. After 30 min at -20°C were added 1.4 ml (13.9 mmol) methyl allyl amine to the white suspension. After 4 h at -20°C the mixture is poured into 50 ml water and extracted with EtOAc. The organic phase is washed with water, dried with Na_2SO_4 and evaporated. The residue is purified via chromatography on silica gel (EtOAc/hexane 1:2). Yield 1.11 g of the methyl ester, which was taken up in 5 ml MeOH and 5 ml 1N NaOH. After stirring for 2h the mixture is acidified with 6 ml 1N HCl and extracted with EtOAc. The organic layer is dried with Na_2SO_4 and evaporated to yield 0.936 g of the title compound as a white solid. LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 2.92 min; MS(ES) MNa^+= 242.2

Example 14: N-Butyl-4-hydroxy-2-methyl-4-((R)-11-methyl-15-oxo-2-oxa-14-aza-bicyclo[14.3.1]icosa-1(19),16(20),17-trien-13-yl)-butyramide

The title compound is obtained similarly to Example 12 as a 3:1 diastereomeric mixture using 3-hex-5-enyloxy-benzoic acid (prepared similarly to 3-(9-decenyloxy)benzoic acid in Lin, H-C et al Macromolecules 1998, 31, 7298) as a starting material in step c.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 6.04 and 6.13 min (1:3 mixture of diastereomers); MS(ES) MNa^+= 497.4

Example 15: N-Butyl-4-hydroxy-2-methyl-4-((R)-9-methyl-13-oxo-2-oxa-12-aza-bicyclo [12.3.1]octadeca-1(17),14(18),15-trien-11-yl)-butyramide

The title compound is obtained as a 5:1 diastereomeric mixture using 3-but-3-enyloxy-benzoic acid (prepared similarly to 3-(9-decenyloxy)benzoic acid in Lin, H-C et al Macromolecules 1998, 31, 7298) as a starting material in step 18c.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.44 min; MS(ES) MNa^+= 469.2

Example 16: (2R,4S)-N-Butyl-4-hydroxy-2-methyl-4-((10R,12S)-10-methyl-14-oxo-2-oxa -13-aza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-12-yl)-butyramide

The title compound is obtained similarly to Example 12 using 3-pent-4-enyloxy-benzoic acid as a starting material in step c (prepared similarly to 3-(9-decenyloxy)benzoic acid in: Lin, H-C et al Macromolecules 1998, 31, 7298).

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.87 min; MS(ES) MNa^+= 483.2

Example 17: (2R,4S)-N-Butyl-4-((4S,7S,9R)-4,9-dimethyl-3,3,5-trioxo-3lambda*6*-thia-6-aza-bicyclo[10.3.1]hexadeca-1(16),12,14-trien-7-yl)-4-hydroxy-2-methyl-butyramide

The title compound is obtained in a similar manner as Example 5, starting from (E)-(5S,8S,10S)-5,10-Dimethyl-8-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-3,3-dioxo-3lambda*6*-thia-7-aza-bicyclo[11.3.1]heptadeca-1(17),11,13,15-tetraen-6-one.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.34 min; MS(ES) MNa^+= 517.2

The starting materials are prepared as follows:

a) (E)-(5S,8S,10S)-5,10-Dimethyl-8-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-3,3-dioxo-3lambda*6*-thia-7-aza-bicyclo[11.3.1]heptadeca-1(17),11,13,15-tetraen-6-one

The title compound is prepared similarly to (E)-(3S,6S,8R)-3,8-Dimethyl-6-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-1,1-dioxo-1lambda*6*-thia-5-aza-cyclohexadec-11-en-4-one, starting from (S)-2-Methyl-N-[(1S,3S)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-3-(3-vinyl-phenylmethanesulfonyl)-propionamide.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.45 min; MS(ES) MNa^+= 442.2

b) (S)-2-Methyl-N-[(1S,3S)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-3-(3-vinyl-phenylmethanesulfonyl)-propionamide

The title compound is prepared similarly to (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-N-[(1S,3R)-3-methyl-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-hept-6-enyl]-propionamide starting from (S)-2-methyl-3-(3-vinyl-phenyl-methane-sulfonyl)-propionic acid and [(S)-3-methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-carbamic acid tert-butyl ester.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.15 min; MS(ES) MNa^+= 470.2

c) [(S)-3-Methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-carbamic acid tert-butyl ester

The title compound is prepared following the procedure described for step e of Example 2.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.09 min; MS(ES) MNa^+= 320.2

d) [(S)-3-Methyl-1-(5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-carbamic acid tert-butyl ester

A mixture of 2.19 g (6.67 mmol) (R)-6-tert-butoxycarbonylamino-4-methyl-6-(5-oxo-tetrahydro-furan-2-yl)-hexanoic acid, 0.293 g (1.46 mmol) copper(II)acetate monohydrate, 0.2 ml pyridine and 5.4 g (12.0 mmol) $Pb(OAc)_4$ in 45 ml benzene is refluxed under nitrogen for 18 h. The mixture is cooled to rt, water is added and the organic phase is washed with

water (3x) and 5% aqueous $NaHCO_3$ (2x). The organic phase is dried with Na_2SO_4, filtered and evaporated. The residue is purified by chromatography on silica gel (EtOAc/hexane 1:6 and 1:4) to yield 0.624 g of the title compound.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.60 min; MS(ES) MNa^+= 306.2

e) (R)-6-tert-Butoxycarbonylamino-4-methyl-6-(5-oxo-tetrahydro-furan-2-yl)-hexanoic acid

2.09 g (6.67 mmol) [(R)-3-Methyl-6-oxo-1-(5-oxo-tetrahydro-furan-2-yl)-hexyl]-carbamic acid tert-butyl ester in the presence of 1.2 g (10 mol) NaH_2PO_4 in 50 ml tBuOH and 10 ml water is subsequently treated with 20 ml of a 2M THF solution of 2-methyl-2-butene and 2.35 g (20.6 mmol) $NaClO_2$ (technical, 80%). After stirring for 10 min the mixture is diluted with EtOAc and brine. The organic phase is dried with $MgSO_4$, filtered and evaporated to yield 2.39 g of (R)-6-tert-butoxycarbonylamino-4-methyl-6-(5-oxo-tetrahydro-furan-2-yl)-hexanoic acid as a resin which is used in the next step without purification.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.71 min; MS(ES) MNa^+= 352.2

f) [(R)-3-Methyl-6-oxo-1-(5-oxo-tetrahydro-furan-2-yl)-hexyl]-carbamic acid tert-butyl ester

A solution of 5.4 g (15.9 mmol) of [(R)-3,7-dimethyl-1-(5-oxo-tetrahydro-furan-2-yl)-oct-6-enyl]-carbamic acid tert-butyl ester (example 1g) in a mixture 200 ml DCM and 10 ml MeOH is cooled to -70°C. After addition of 0.63 g (7.5 mmol) $NaHCO_3$ a stream of O_3 in O_2 is passed through the stirred mixture till a blue color persisted. The excess ozone is removed by passing through more dioxygen. After addition of 5.0 g (19 mmol) triphenylphosphine the mixture is allowed to warm up at rt and stirred for 4 h. The mixture is filtered and concentrated in vacuo. Chromatography on silica gel (EtOAc/Hexane 1:1) gave 2.5 gram of the title aldehyde.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.14 min; MS(ES) MNa^+= 336.2

g) (S)-2-Methyl-3-(3-vinyl-phenylmethanesulfonyl)-propionic acid

A mixture of 1.84 g (5 mmol), 5 ml 1N NaOH, 1.38 g (10 mmol) K_2CO_3 and 0.072 mg $Pd(PPh_3)_4$ (0.25 mmol) in 5 ml water and 50 ml DME is heated at 80°C under nitrogen. After cooling down the mixture is acidified with 20 ml 2N HCl and extracted with 150 ml TBME. The organic phase is dried with Na_2SO_4, filtered and evaporated to yield of 1.47 g of the title compound that is used in the next step without purification.

LC (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.75 min; MS(API-ES) $[M-H]^-$= 267.0

h) (S)-3-(3-Iodo-phenylmethanesulfonyl)-2-methyl-propionic acid

The title compound is prepared similarly to (S)-3-(hex-5-ene-1-sulfonyl)-2-methyl-propionic acid but starting from (S)-3-(3-iodo-benzylsulfanyl)-2-methyl-propionic acid instead of (S)-3-hex-5-enylsulfanyl-2-methyl-propionic acid.

LC (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 3.97 min; MS(API-ES) $[M-H]^-$= 367.0

i) (S)-3-(3-Iodo-benzylsulfanyl)-2-methyl-propionic acid

The title compound is prepared similarly to (S)-3-hex-5-enylsulfanyl-2-methyl-propionic acid, using 1-bromomethyl-3-iodo-benzene instead of 6-bromo-hex-1-ene.

LC (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 5.11 min; MS(API-ES) $[M-H]^-$= 335.0

Example 18: (2R,4S)-N-Butyl-4-((9S,12S,14R)-9,14-dimethyl-7,10-dioxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5-oxa-8,11-diaza-benzocyclopentadecen-12-yl)-4-hydroxy-2-methyl-butyramide

The title compound is prepared similarly to Example 2, using (2-allyl-phenoxy)-acetic acid instead of (2S)-*tert*-butoxycarbonyl-2-amino-6-heptenoic acid in step c and starting from [(S)-3-methyl-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-pent-4-enyl]-carbamic acid tert-butyl ester in step d.

LC/MS (Nucleosil C-18HD, 4x70 mm, 3µM, 20-100% MeCN (6 min), 100% MeCN (1.5 min)): 4.8 min.

Example 19: 6(R/S)-[1(R/S)-Hydroxy-2-(3-isopropyl-benzylamino)-ethyl]-3(S),8(R)-dimethyl-1,1-dioxo-1lambda*6*-thia-5-aza-cyclohexadecan-4-one

Rf: (DCM/methanol 9:1): 0.20
MS (ES): 509.8 [M+H].

The title compound is prepared similarly to Example 1, but starting from N-(1(R/S)-Cyano-3(R)-methyl-hept-6-enyl)-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide in step k instead of hept-6-enoic acid {1(S)-[1(R/S)-(2-chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enylcarbamoyl]-ethyl}-methyl-amide.

The staring materials can be prepared as described hereafter:

a) N-(1(R/S)-Cyano-3(R)-methyl-hept-6-enyl)-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide

To a solution of (S)-3-hex-5-enylsulfanyl-2-methyl-propionic acid (1.57 g, 7.46 mmol, 1.1 eq) and HOBt (1.65 g, 10.44 mmol, 1.4 eq) in DCM (34 ml) is added EDC (1.72 g, 8.95 mmol, 1.2 eq) at 0 °C, then after 10 min 2(R/S)-amino-4(R)-methyl-oct-7-enenitrile (1.03 g, 6.78 mmol). The mixture is allowed to warm to rt and stirring is continued at rt for 17 h. The reaction mixture is then cooled to 0 °C, 0.5 M HCl (68 ml) is added and the layers are separated. The aqueous phase is extracted with DCM/ethanol 8:2 (2 × 68 ml), the combined organic layers are washed with 1 M potassium bicarbonate (68 ml), water (68 ml), dried with sodium sulfate and evaporated to yield the desired product as a yellowish oil (2.76 g, approx. 1:1 mixture of diastereomers), which is used for the next step without further purification.
Rf: (DCM/methanol = 95:5): 0.73,
MS (LC/MS): 337.0 [M+H], 359.0 [M+Na].

b) 2(R/S)-(3-Hex-5-enylsulfanyl-2-(S)-methyl-proppionylamino-4(R)-methyl-oct-7-enoic acid methyl ester

To a solution of N-(1(R/S)-cyano-3(R)-methyl-hept-6-enyl)-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide (2.76 g, 6.78 mmol) in methanol (20 ml) is added slowly 5 M HCl in Et_2O (27 ml, 135 mmol, 20 eq) at 0 °C. The mixture is allowed to warm to rt and is stirred at rt for 1 h. Water (95 ml) is added at 0 °C, the mixture is allowed to warm to rt and stirring is continued at rt for 30 min. The mixture is extracted with DCM (3 × 136 ml), the combined organic layers are washed with 1 M potassium bicarbonate (136 ml), water (136 ml), dried with sodium sulfate and evaporated. Purification by chromatography on silica gel (cyclohexane/EtOAc

8:2) gives the desired product as a yellowish oil (1.46 g, approx. 1:1 mixture of diastereomers).
Rf: (cyclohexane/EtOAc = 8:2): 0.33 / 0.24,
MS (EI+): 370.0 [M+H],
^{1}H-NMR (400 MHz, d6-DMSO, 2 diastereomers): 8.25-8.18 (m, 1H), 5.84-5.67 (m, 2H), 4.48-4.27 (m, 1H), 3.60 (d, 3H), 2.72-2.34 (m, 5H), 2.11-1.89 (m, 4H), 1.69-1.10 (m, 9H), 1.06 (t, 3H), 0.88 (d, 1.5H), 0.84 (m, 1.5H).

c) N-[1(R/S)-(2-Chloro-acetyl)-3(R)-methyl-hept-6-enyl]-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide

Chloroiodomethane (1.15 ml, 2.79 g, 15.8 mmol, 4.0 eq) is added to a solution of 2(R/S)-(3-hex-5-enylsulfanyl-2-(S)-methyl-proppionylamino-4(R)-methyl-oct-7-enoic acid methyl ester (1.46 g, 3.95 mmol) in THF (40 ml) under an argon atmosphere, at -78 °C. LDA (1.44 M in THF, 13.7 ml, 19.8 mmol, 5 eq) is added dropwise while the temperature of the reaction mixture is maintained below -68 °C, and the mixture is stirred for an additional 30 min. Glacial acetic acid (5.9 ml, 103 mmol) is then added dropwise while the temperature is maintained below -65 °C, stirring is continued for 15 min at -78 °C then the mixture is allowed to warm to 0 °C and a half-saturated aqueous sodium chloride solution is added (60 ml). The mixture is extracted with TBME (2 × 60 ml), the combined organic layers are washed with 1 M sodium bicarbonate (60 ml), 1 M sodium sulfite (60 ml) and water (60 ml), dried with sodium sulfate and evaporated. The desired product is obtained as a brownish oil (2.86 g, approx. 1:1 mixture of diastereomers), and used for the next step without further purification.
Rf: (cyclohexane/EtOAc = 8:2): 0.36,
MS (LC/MS): 387.9/389.9 [M+H].

d) N-[1(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enyl]-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide

A solution of N-[1(R/S)-(2-chloro-acetyl)-3(R)-methyl-hept-6-enyl]-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide (2.86 g, 3.95 mmol) in ethanol (24 ml) is added to a suspension of sodium borohydride (299 mg, 7.9 mmol, 2 eq) in ethanol (87 ml) at -78 °C. The temperature is kept below -75 °C during the addition and the mixture is stirred for an additional hour. 1 M HCl (20 ml) is added at -78 °C and the mixture is allowed to warm to rt. After evaporation of the ethanol, 1 M HCl (40 ml) is added and the mixture extracted with EtOAc (2 × 40 ml). The

combined organic layers are washed with 1 M HCl (40 ml) and a half-saturated aqueous sodium chloride solution (40 ml), dried with sodium sulfate and evaporated. Purification by chromatography on silica gel (cyclohexane/EtOAc 8:2) yields the desired product as a brown oil (1.28 g, approx. 1:1 mixture of diastereomers).
Rf: (cyclohexane/EtOAc 8:2): 0.18,
MS (EI+): 412.0 [M+Na],
^{1}H-NMR (400 MHz, d6-DMSO, 2 diastereomers): 7.70 (d, 0.5H), 7.64 (d, 0.5H), 5.84-5.66 (m, 2H), 5.30-5.24 (m, 1H), 5.04-4.87 (m, 4H), 3.82-3.72 (m, 1H), 3.62-3.35 (m, 3H), 2.64-2.58 (m, 1H), 2.52-2.38 (m, 6H), 2.09-1.95 (m, 3H), 1.56-1.19 (m, 8H), 1.05 (t, 3H), 0.85 (d, 1.5H), 0.80 (m, 1.5H).

e) N-[1(R/S)-(2-Chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enyl]-3-(hex-5-ene-1-sulfonyl)-2(S)-methyl-propionamide

To a solution of N-[1(R/S)-(2-chloro-1(R/S)-hydroxy-ethyl)-3(R)-methyl-hept-6-enyl]-3-hex-5-enylsulfanyl-2(S)-methyl-propionamide (1.28 g, 3.29 mmol) in acetonitrile (11 ml) and water (3 ml) is added oxone® (2.02 g, 3.29 mmol) at 0 °C. The mixture is stirred at rt for 2 h, then more oxone® (1.21 g, 1.98 mmol) is added and the mixture stirred at rt for 3 days. Water (26 ml) is added and the mixture extracted with EtOAc (2 × 26 ml), the combined organic layers are washed with water (26 ml), dried with sodium sulfate and evaporated. Purification by chromatography on silica gel (cyclohexane/EtOAc 6:4) gives the desired product as a brown oil (757 mg, approx. 1:1 mixture of diastereomers).
Rf: (cyclohexane/EtOAc = 6/4): 0.21,
MS (EI+): 422.0 [M+H],
^{1}H-NMR (400 MHz, d6-DMSO, 2 diastereomers): 7.89 (d, 0.5H), 7.84 (d, 0.5H), 5.84-5.67 (m, 2H), 5.31 (d, 0.5H), 5.23 (d, 0.5H), 5.07-4.88 (m, 4H), 3.79-3.70 (m, 1H), 3.60-3.36 (m, 3H), 3.08-2.85 (m, 4H), 2.09-1.99 (m, 3H), 1.70-1.62 (m, 2H), 1.49-1.12 (m, 12H), 0.85 (d, 1.5H), 0.80 (m, 1.5H).

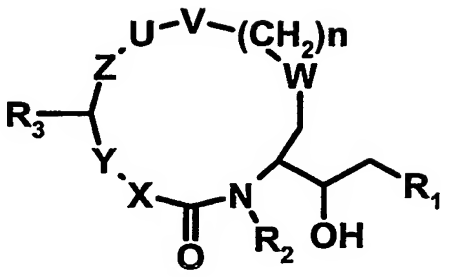
The following compound is obtained by a similar procedure:

<u>Example 19a:</u> 6(R/S)-[1(R/S)-Hydroxy-2-(1,2,3,4-tetrahydronaphthalen-1(S)-ylamino)-ethyl]-3(S),8(R)-dimethyl-1,1-dioxo-1lambda*6*-thia-5-aza-cyclohexadecan-4-one

Rf: (DCM/methanol = 90/10): 0.31
MS (ES): 507.8 [M+H].

Claims

1. A compound of formula I



I

wherein

R_1 is $CH(R_e)CONR_aR_b$ or $(CH_2)_kNR_cR_d$, wherein

k is 0, 1 or 2,

R_a and R_b, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl,

R_c and R_d, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl, heteroaryl(C_{1-4})alkyl, chroman-4-yl, 1,2,3,4-tetrahydro-quinolin-4-yl, 1,2,3,4-tetrahydro-naphthalen-1-yl, thiochroman-4-yl, 1,1-dioxo-1lambda*6*-thiochroman-4-yl, isochroman-4-yl, 1,2,3,4-tetrahydro-isoquinolin-4-yl, isothiochroman-4-yl, 2,2-dioxo-2lambda*6*-isothiochroman-4-yl, 2,2-dioxo-1,2,3,4-tetrahydro-2lambda*6*-benzo[c][1,2]thiazin-4-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-benzo[e][1,2]thiazin-4-yl, 2,2-dioxo-3,4-dihydro-2H-2lambda*6*-benzo[e][1,2]oxathiin-4-yl, 1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-benzo[e][1,2]thiazin-4-yl, 2,3,4,5-tetrahydro-benzo[b]oxepin-5-ylamine or 1,3,4,5-tetrahydro-benzo[c]oxepin-5-ylamine, or

R_a, and R_b, or R_c and R_d, together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidino, morpholino or piperazinyl group, and

R_e is optionally substituted (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl,

R_2 is hydrogen or (C_{1-4})alkyl,

R_3 is hydrogen or an optionally substituted (C_{1-6})alkylOCONH, (C_{3-7})cycloalkylOCONH, (C_{3-7})cycloalkyl(C_{1-4})alkylOCONH, aryl(C_{1-4})alkylOCONH, heteroaryl(C_{1-4})alkylOCONH, (C_{1-4})alkylCONH, (C_{3-7})cycloalkylCONH, heteroarylCONH, arylCONH, aryl(C_{1-4}) alkylCONH or heteroaryl(C_{1-4})alkylCONH group,

U is (C_{1-3})alkylenoxy, (C_{1-3})alkylen, NR_g or an aromatic or heteroaromatic ring, optionally substituted with halogen, (C_{1-4})alkoxy, hydroxyl or (C_{1-4})alkyl, whereby Z and V are in ortho or meta position to each other, wherein R_g is hydrogen or (C_{1-4})alkyl,

V is a CHCH, $CH_2CH(OH)$, $CH(OH)CH_2$, CH_2CH_2, or CR_hR_iCH group, wherein R_h and R_i, independently, are hydrogen or (C_{1-4})alkyl,

W is (C_{1-2})alkylen, $CHCH_3$, O, S, SO_2, CO, COO, OCO, NR_fCO, $CONR_f$ or NR_f, wherein R_f is hydrogen or (C_{1-4})alkyl,

X is an optionally substituted (C_{1-4})alkylidene, (C_{1-4})alkylene, (C_{3-7})cycloalkylene, piperidin-diyl, pyrrolidin-diyl, benzothiazole-4,6-diyl, benzoxazole-4,6-diyl, 1H-benzotriazole-4,6-diyl, imidazo[1,2-a]pyridine-6,8-diyl, benzo[1,2,5]oxadiazole-4,6-diyl, benzo[1,2,5]thiadiazole-4,6-diyl, 1H-indole-5,7-diyl, 1H-indole-4,6-diyl, 1H-benzoimidazole-4,6-diyl or 1H-indazole-1,6-diyl, or X is an optionally substituted aromatic or heteroaromatic ring, whereby Y and $CONR_2$ are in meta position to each other

Y is a bond, oxygen, SO_2, SO_2NR_g, NR_g, CR_gOH, $CONR_g$ or NR_gCO group,

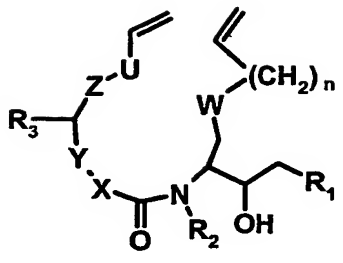
Z is oxygen, CH_2 or a bond, and

n is 0 to 3,

the number of atoms included in the macrocyclic ring being 14 to 17,

in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which includes the steps of cyclisation by metathesis of a compound of formula II



II

wherein R_1, R_2, R_3, U, W, X, Y, Z and n are as defined in claim I, in the presence of a catalyst, optionally further reducing, oxidizing or functionalizing the resulting double bond, and recovering the so obtained compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

5. A pharmaceutical composition comprising a compound of claim 1 in free base of pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical, for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

8. A method for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation in a subject in need of such treatment, which

comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound of claim 1 in free base of pharmaceutically acceptable acid addition salt form and a second drug substance, for simultaneous or sequential administration.